TABLE I
Intercountry Analysis
Immunization Schedule Versus Incidence of Type I Diabetes Mellitus

Group	*Immunization Schedule*		Year	Incidence of Diabetes		Non-Weighted Group Mean	P Values		
		(reference)			(reference)				
1	***No Pertussis, No BCG***					14.5			
	Italy, Lombardi Region	(6,13)	1988	6.8	(1)				
	Italy, Lazio Region	(6,13)	1987	6.5	(1)				
	Italy, Sardinia	(6,13)	1987	30.2	(1)				
2	***Pertussis, BCG before 2 months***					7.45	X		
	Republic of Ireland	(6)	1988	6.8	(2)				
	France	(6)	1990	7.8	(1)				
	Austria	(6)	1989	7.7	(1)				
	Portugal	(6)	1986	7.5	(1)				
3	***Pertussis, No BCG***					10.92	(P<0.02)	X	
	Iceland	(7)	1980-1989	10.8	(3)				
	Netherlands	(6)	1989	11	(1)				
	Spain, Catelinia	(6)	1986	10.6	(1)				
	Spain, Madrid	(6)	1985-1988	10.9	(16)				
	Belgium	(8)	1989	9.8	(1)				
	Luxembourg	(6)	1989	12.4	(1)				
4	***Pertussis, BCG Vaccination School Age***					20.01	P<.0001	P<.005	X
	England, Oxford	(6)	1988	16.4	(1)				
	Northern Ireland	(6)	1988	16.6	(2)				
	Scotland	(6)	1988	19.8	(2)				
	Denmark	(6,12)	1990	21.5	(1)				
	Norway	(15)	1989	20.8	(1)				
	Malta	(9)	1980-1987	(13.6+)	(4)				
	Sweden	(6,10,11)	1987	25	(5)				
5	***Pertussis, Hib, BCG Vaccination at 3 months and School Age***					42.9	P<.0001	P<.0001	P<.0001
	Finland	(6,14)	1988	42.9	(1)				

Incidences of type I diabetes mellitus are reported as yearly figures per 100,000 children as recorded in the references indicated. Statistics were generated from unweighted group means using a normal approximation to the poisson distribution. All statistics shown where highly significant using T=1 with the exception of group 3 where (P<0.02) was calculated using T=4. Sardinia was the only major exception to the trend as discussed in the text. The incidence of diabetes in Malta was significantly underestimated as discussed in reference 4. The immunization schedule of Sweden has changed during the 15 years prior to 1987. Most notably the pertussis vaccination was discontinued in 1979.

References

1. Lancet 339:905-909, 1992
2. British Medical Journal 302:443-447, 1991
3. Diabetologia 35:880-883, 1992
4. Diabetic Medicine 6:228-231, 1989
5. International Journal of Epidemiology 19:141-146, 1990
6. World Health Organization, Working Group on Immunization of Tourists and other Travelers Venice,November 1990, By B. Bytchenko
7. Vaccination policy and status in Iceland
8. Symp.Series immunobiol.Standard, 22:223-225, 1973
9. Personel Communication Malta pediatrician, #011-356-241-251
10. Pediatr.Infect.Dis J. 6:364-371, 1987
11. Personel Communication Dr. Ingrid Trolin, Uppsala Sweden (46) 18 17 46 61
12. Symp.Series immunobiol.Standard, 22:235-237, 1973
13. Pediatr.Infect.Dis.J. 11:653-661,1992
14. N.Engl.J.Med 323:1381-1387, 1990
15. Tubercle 69:119-123, 1988
16. Diabetologia 33:422-424, 1990

Table II
Incidence of Type I Diabetes in Finland

Age Group	Years	N	Incidence of Diabetes Mellitus	% Change Incidence	P values	
0-4	1970-76	262	11.8		X	
	1977-79	174	19.3	63.6%	P<0.001	
	1980-82	152	16	-17.1%	P<0.005	X
	1987-89	243	25.9	61.9%	P<0.0001	P<0.0001
5-9	1970-76	729	27.6		X	
	1977-79	304	32	15.9%	P<0.05	
	1980-82	299	33	3.1%	P<0.02	X
	1987-89	382	39.3	19.0%	P<0.0001	P<0.05
10-14	1970-76	1047	37.5		X	
	1977-79	421	37.5	0%	N.S.	
	1980-82	399	38.6	2.93%	N.S.	X
	1987-89	389	40.6	5.2%	N.S.	N.S.

Incidences of type I diabetes mellitus are reported as yearly figures per 100,000 children as recorded in the references indicated. The per cent change in incidence was calculated using the incidence in the prior year as the reference. Statistics were recorded as reported in the references when available. Statistics not reported were calculated using a normal approximation to the poisson distribution . Differences that were not statistically significant are marked N.S.

References

Diabetologia 35:70-76, 1992
Diabetes Care 8 Suppl 1:10-16, 1985

Table III
Incidence of Type I Diabetes Mellitus
Age 0-4, Allegheny County, Pennsylvania

Years	Incidence of Diabetes Mellitus	% Change Incidence	P Values
1965-1969	6.75		X
1970-1974	6.375	-5.55%	N.S.
1975-1979	2.625	-58.82%	P<.001
1980-1984	9.875	276.19%	P<.02
1985-1989	16.125	63.29%	P<.0001

Total # of cases 183

Incidences of type I diabetes mellitus are reported as yearly figures per 100,000 children as recorded in the reference indicated. The per cent change in the incidence was calculated using the incidence in the prior year as the reference. Statistics were calculated using a normal approximation to the poisson distribution . The results show a highly statistically significant decline in the incidence of type I diabetes mellitus in the years 1975-1979 as well as statistically significant rise during the years 1980-1989. Differences that were not statistically significant were marked N.S.

Reference
Diabetes Care 16:1606-1611,1993

Table IV
Cumulative Incidence of Type I Diabetes Mellitus
Danish Military Recruits Age 18

Year of Birth	# of Type I Diabetics	Cumulative Incidence Diabetes per 1000	P value	Smallpox Cases Western Europe
1960	189	1.85		1
1961	167	1.76		79
1962	96	1.11	P<0.05	51
1963	188	1.5		28
1964	198	1.83		0
1965	203	1.93		1
1966	184	1.71	N.S.	72
1967	219	2.07		2
1968	194	1.96		2
1969	264	2.11		0
1970	234	2.12		22

Cumulative incidences of type I diabetes mellitus in Danish military recruits under 19 years of age are reported per 1000 recruits as recorded in the reference indicated. Statistics were calculated by the authors in the reference. The results show a statistically significant decline in the incidence of type I diabetes mellitus in the years 1961-1963 which corresponded to a smallpox epidemic. The decline in the incidence of diabetes in 1962 followed the epidemic of 1961. The incidence of diabetes also declined in 1966 during a second smallpox epidemic. The later was not statistically significant, N.S.

Reference
Diabetologia 35:139-142, 1992
WHO Chronicle 16:302-305, 1962
Vasile Tudor and Ioan Strati, 1977, Smallpox : Cholera. Abacus Press, Kent England.

Table V
Potential Immunization Schedules

Week	Schedule 1	Schedule 2	Schedule 3	Schedule 4
0 (birth)	DTP,Hib,HepB,IPV,MMR,NPI		DTP,Hib,HepB,IPV,MMR,NPI	DT,Hib,HepB,IPV
1				
2	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		DTP,Hib,HepB,IPV,MMR
3			DTP,Hib,HepB,IPV,MMR,NPI	
4	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		DTP,Hib,HepB,IPV,MMR
5				
6	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,IPV,MMR
7				
8	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		
9			DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,IPV,MMR
10	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		
11				
12	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR	DTP,Hib,HepB,IPV,MMR	DTP,Hib,HepB,IPV,MMR
13				
14	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		
15			DTP,Hib,IPV,MMR	DTP,Hib,HepB,IPV,MMR
16	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR		
17				
18	DTP,Hib,HepB,IPV,MMR,NPI	DTP,Hib,HepB,OPV,MMR	DTP,Hib,IPV,MMR	DTP,Hib,HepB,IPV,MMR

The four immunization schedules above are nonlimiting examples of immunization schedules that can be used to reduce the incidence of diabetes as compared to standard immunization schedules listed in the specifications. The following appreviations are used above: DTP - diptheria, tetanus, pertussis; Hib-Haemophilus influenza B; HepB - hepatitis B; IPV - inactivated polio virus; OPV - oral polio virus, MMR - measles mumps rubella, NPI - nonpediatric immunogen.

Table VI
Types of Vaccines Affecting Type I Diabetes

Vaccine	Live or Killed	Bacteria Virus or Toxoid	Adjuvant	Whole Cell or Purified	Protein or Carbohydrate	Animal Data	Epidemiology Data
Anthrax	killed	bacteria	yes	purified	both	yes	no
Plague	killed	bacteria	none	whole cell	both	yes	no
DT	killed	toxoid	yes	purified	protein	yes	no
Pertussis	killed	bacteria	yes	whole cell	both	yes	yes
Hib	killed	bacteria	yes	purified	carbohydrate	no	yes
BCG	live	bacteria	none	whole cell	both	yes	yes
Smallpox	live	virus	none	whole cell	both	no	yes
MMR	live	virus	none	whole cell	both	no	yes

A variety of very different classes of human vaccines have been shown to modulate the development of type I diabetes mellitus. Only the BCG vaccine has been shown to contain an immunogen that cross reacts to an autoantigen assosiated with type I diabetes mellitus.

Graph I

BB Rats

DTP + Anthrax vaccine